ATTORNEY DOCKET NO. 2003028-0048 (ARIAD 331 D US1)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Schreiber & Crabtree	Examiner:	Vogel
Serial No.:	09/834,424	Art Unit:	1636
Filing Date:	April 13, 2001	Conf. No.:	5917
Title:	METHODS AND MATERIALS INVOLVING DIMERIZATION-MEDIATED REGULATION OF BIOLOGICAL EVENTS		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION UNDER 37 C.F.R. § 1.132

I, Timothy P. Clackson, Ph.D., declare as follows:

1. I am the Senior Vice President and Chief Scientific Officer at ARIAD Pharmaceuticals, Inc., Cambridge, Massachusetts, the licensee of U.S. Serial No. 09/834,424, filed April 13, 2001 (the '424 application). I have served in this role since September 2003. Previously, I served as Senior Vice President, Science and Technology from June 2002 to September 2003, as Vice President, Gene Therapy and Genomics from June 2000 to June 2002, as Director, Gene Therapy from August 1999 to June 2000 and as Department Head, Gene Therapy Biology from March 1999 to August 1999.

2. I received my B.A. degree in Biochemistry from the University of Oxford in 1987 and my Ph.D. degree in Biology from the University of Cambridge in 1991, for research conducted at the MRC Laboratory of Molecular Biology into antibody engineering and the development of phage display technology. I was a postdoctoral fellow at Genentech, Inc. from 1991 to 1994, where I studied the molecular basis for human growth hormone function. I have authored or co-authored numerous research articles in the field of receptor dimerization and regulation of

biological events, including Clackson and Wells, "A hot spot of binding energy in a hormone-receptor interface," *Science* 267:383–386 (1995), which has been cited over 800 times. A copy of my curriculum vitae with a full list of publications is attached hereto as Exhibit A.

3. I have reviewed the specification and claims of the '424 application as well as the Office Action mailed on May 29, 2009 (hereinafter "the current Office Action"). I understand that the Examiner has rejected all the pending claims under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description and enablement requirements.

4. I further understand that the Board of Patent Appeals and Interferences (BPAI) rendered a decision on October 1, 2008 reversing an earlier written description rejection in this case and that the Examiner mailed a Notice of Allowance on December 2, 2008. I also understand that a Request for Continued examination was then filed in the '424 application on March 2, 2009 with an Information Disclosure Statement that cited *inter alia* references that had been submitted in opposition proceedings for a related European application. I further understand that in the current Office Action, the Examiner has reinstated the written description rejection and has levied a new enablement rejection under 35 U.S.C. § 112, first paragraph in light of Connolly et al.[1], one of the references that was cited in the Information Disclosure Statement (hereinafter "Connolly"). In particular, I understand that the Examiner has taken the position that Connolly provides evidence of the state of and unpredictability in the art.

5. I understand that the Examiner has argued that Connolly provides evidence that "the relationship of structure of a small, non-peptidic molecule to its function in dimerization, even where affinity is high for one subunit of the receptor at a time, was not well enough understood at the time of filing to have permitted one of skill in the art to have recognized that Applicants were in possession of the full scope of the claims" (page 6 of the current Office Action). I also understand that the Examiner has relied on Connolly as evidence that "the post-filing date art

[1] Connolly et al., "Synthesis and Erythropoietin Receptor Binding Affinities of *N,N*-Disubstituted Amino Acids," *Bioorganic & Medicinal Chemistry Letters* 10:1995-1999 (2000) , submitted with the Information Disclosure Statement filed on March 2, 2009.

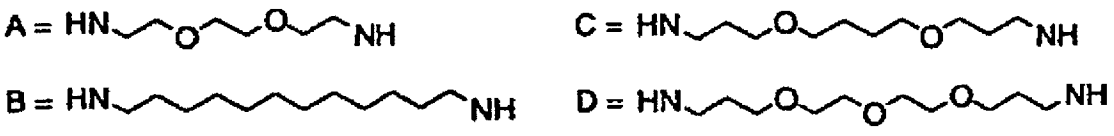
showed great unpredictability in the ability to prepare an agent including a first and second non-peptidic moiety that each bind to one of the cell surface receptor molecules, and which effects a biological event mediated by the association of the cell surface receptor molecules" (pages 10-11 of the current Office Action).

6. I have reviewed Connolly and, for reasons that are set forth below and that were discussed with the Examiner during a telephone Interview on September 23, 2009, I find that it is not representative of what was known in the art as of the effective filing date of the '424 application. As a result, it is my opinion that Connolly should not be relied on as evidence of the state of or unpredictability in the art and that the BPAI would not reverse its earlier decision based solely on the teachings of Connolly.

7. Connolly describes experiments that were performed in an attempt to produce dimeric compounds that can dimerize and thereby activate the erythropoietin (EPO) receptor. Connolly begins by using a cell-free *in vitro* binding assay to screen a set of monomeric compounds for binding to the EPO receptor (see Tables 1 and 2). Specifically, the compounds were tested for their ability to displace EPO from immobilized EPO receptor extracellular domains. Having identified some "moderately potent" monomeric compounds in the *in vitro* binding assay they proceeded to create dimeric analogues by connecting them via a hydrocarbon or polyether linking group as shown in Table 4. These dimeric analogues were then tested using the same cell-free *in vitro* binding assay to identify those with the greatest binding affinity for the EPO receptor (see Table 4). The authors then proceeded directly to test the "best" dimeric analogues for their ability to promote EPO receptor triggered proliferation in a cell-based assay (see paragraph spanning pp. 1997-1998). It is notable that Connolly provides no details whatsoever regarding this last set of experiments (e.g., concentrations tested, controls performed, etc.). Connolly concludes that "despite EPO receptor binding affinity on par with that of EPO-mimetic peptide EMP1 (1), the best 'dimeric' analogues [...] did not promote proliferation in the FDC-P1 cell assay. Apparently, the tethered construct [...] was not flexible enough or could not span the distance required to bring together two EPO receptor molecules. The additional binding affinity

gained by the 'dimer' construct was likely due to added nonspecific hydrophobic interactions outside the EPO binding pocket of EBP or the EPO receptor."

8. It is my opinion that Connolly describes an incomplete and consequently flawed set of experiments. The set of experiments is not representative of the expected level of skill in this field at that time, and the reported results and discussion do not support the conclusions relied upon by the Examiner. While the person of ordinary skill in this field may have been expected to anticipate foreseeable experimental issues or at least to investigate and react to apparently negative results, Connolly disclosed no effort whatsoever to look beyond their initial choice of linkers used to make dimeric analogues or to make a routine investigation of their apparent experimental failure. In describing their choice of linkers, Connolly even acknowledged that they used "a series of commercially available diamines" that "proved to be a convenient set of reagents," confirming that convenience and availability were the primary factors that determined their choice. The fact that Connolly did not try any other linker is particularly striking, as it would have been considered routine to test a diverse set of linking groups, certainly after their apparent failure. The four linkers A, B, C, and D that Connolly used are shown in Table 4 and reproduced below:



These linkers do not comprise a diverse set. Linker B contains a long hydrocarbon chain that is extremely hydrophobic and would therefore be disfavored because of the strong likelihood that the linker would (a) collapse on itself and/or (b) bury itself into the hydrophobic cell membrane, rather than interact with cell surface EPO receptors. Connolly comments on the possibility of hydrophobic collapse on page 1997: "[t]he hydrophobic [linker B] was associated with the lower affinity 'dimers' [...] possibly due to poor access to the EPO binding site resulting from hydrophobic collapse of the linker." Linkers A, C, and D are all polyethers with similar structures that are also relatively hydrophobic. Thus, Connolly comments on page 1998 that "[t]he additional binding affinity gained by the 'dimer' construct was likely due to added

nonspecific hydrophobic interactions outside the EPO binding pocket of [the EPO receptor extracellular domain] or the EPO receptor." Connolly also implicitly acknowledges in the same paragraph that lack of linker diversity likely contributed to the absence of cell proliferation "[a]pparently, the tethered construct [...] was not flexible enough or could not span the distance required to bring together two EPO receptor molecules."

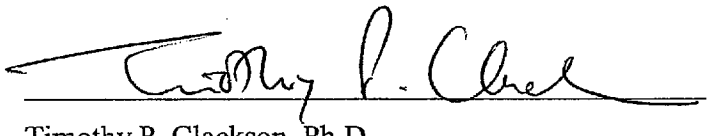
9. I was also surprised to see that the authors interpreted their negative results in the cell-based proliferation assay as evidence that their dimeric analogues were unable to activate EPO receptors despite having high binding affinities. This conclusion ignores the fact that the negative results could just as equally have resulted from a failure to bind the EPO receptor in the more complex environment of a cell-based assay (rather than from a failure to activate after hypothetical binding). As discussed above, and as was evident then, such a failure to bind could easily be caused by using a linker that is too hydrophobic. Connolly should have performed a set of routine control experiments to confirm that the dimeric analogues actually bind the EPO receptor in a cell-based assay. Having neglected to do so before testing them in the cell-based proliferation assay, they certainly should have done so after having obtained what they interpreted as negative results in the cell-based proliferation assay. Others working in the field would have considered it necessary to perform such a control experiment in order to properly interpret absence of positive results in the cell-based proliferation assay, as binding to a receptor in a cell-free *in vitro* system does not automatically connote binding to the same receptor when presented on a cell.

10. As discussed during the telephone Interview with Examiner Vogel on September 23, 2009, Connolly does not provide any details as to how the cell proliferation assays were actually performed. This is significant because factors such as the concentration of dimeric analogues may have affected the outcome of the experiment. Indeed, as was well known in the art, if cell surface receptor dimerization is tested at various concentrations of dimerizer, an approximately bell-shaped curve is typically observed. When the concentration of dimerizer is too low, there are not enough dimerizers to trigger dimerization. When the concentration of dimerizer is too high, the dimerizers saturate the receptors and thereby prevent pairs of receptors from becoming

connected by a single dimerizer. At high concentration the dimerizer may also be toxic to the cells. Thus, there is an optimal concentration of dimerizers for inducing cell surface receptor dimerization. Connolly do not disclose the concentration(s) they used to test their dimeric analogies, let alone whether they tested different concentrations. Thus, it is entirely possible that Connolly had a working dimeric analogue but tested it at a concentration that was either above or below the effective level for measurement in their assay.

11. For all these reasons, it is my opinion that a person of ordinary skill in the art would not consider that Connolly provides an indication of the state of the art or evidence of the unpredictability in the art. Instead, he or she would view Connolly as an unfinished or flawed research project that teaches very little and may even be a false negative result.

12. I, Timothy P. Clackson, declare that all statements made herein of my own knowledge are true and that these statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like are made punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or any patents that may issue thereon.



Timothy P. Clackson, Ph.D.

November 20, 2009

Date